REMARKS

Claims 1, 19 and 23 have been amended. Claims 1-24 are in the application. However, claims 3, 4, 7 and 9-18 remain withdrawn from consideration pursuant to an election of species requirement, and therefore should be added back into the application upon finding that the independent claims are allowable.

Attached hereto is a marked-up version of the changes made to the claims by the above amendments. In the attached marked-up version of the claim amendments, additions are underlined and deletions are bracketed.

Restriction Under 35 U.S.C. §112

Claims 1, 2, 5, 6, 8 and 19-24 have been rejected under 35 U.S.C. §112, second paragraph. First, the Examiner has requested that Applicants replace the expression "substituents a" with the expression - -substituents α- -. In response, Applicants have amended the claims as requested.

In claim 1, last line, the Examiner has requested that Applicants replace the word "salts" with the word "salt" because "the claim is drawn to just one compound (at a time), or a salt thereof." Applicants agree that the claim is directed to a compound having the stated formula or a salt thereof. However, the appropriate way to claim the subject matter is to claim the compound and salts thereof, rather than to claim the compound or a salt thereof. Even less appropriate is to claim a compound and a salt thereof. This type of claim would be directed to a composition containing both the claimed compound and a salt thereof. The Examiner's request would render the claims worthless to the extent that a competitor could make, use and sell the invention with impunity by either using only salts of the claimed compound or by using only the compound in its base form. Applicants request that the Examiner review the enclosed copy of claim 1 of U.S. Patent No. 6,423,870, which correctly claims a compound having a specified formula and "their enantiomers and diastereoisomers, and addition salts thereof." The owners of the enclosed patent and Applicants are both correctly claiming compounds having a specified formula and all salts thereof, not a compound having the stated formula and/or a salt thereof. Upon further consideration it is believed that the Examiner will agree

that the word "salts" is definite and correct, and that replacement of the word "salts" with the word "salt" would be incorrect and render the claims indefinite, and/or would unduly limit the scope of the claims.

The Examiner has again stated that the expression "a simple heteroatom-containing group" is indefinite. Applicants respectfully disagree. However, Applicants have deleted the word "simple" from the expression at issue to eliminate any indefiniteness associated with determining whether a heteroatom-containing group is simple or not simple.

The expression "heteroatom" appears frequently in the literature, including test books used to teach organic chemistry in major universities. For example, see the enclosed page 1059 of *Organic Chemistry, 6TH Edition*, Fessenden, Ralph J. and Fessenden, Joan S., Brooks/Cole Publishing Company (1998), which uses the expression "heteroatoms" to describe non-carbon atoms in the main chain of an organic compound (namely 2, 5, 8-trioxadecane). Please also consider the enclosed page 1061 of *Webster's Third New International Dictionary*, G & C Merriam Company, Springfield, Massachusetts (1971), which defines the word "hetero" as "relating to or being an atom or element other than the predominating or significant one (as carbon) esp. in a ring of a molecule or compound (atom such as nitrogen or oxygen)." Clearly, the expression "heteroatoms" is consistently used in the literature to refer to atoms in a molecule which are different from the predominant atom, and most typically atoms other than carbon in an organic chain or ring. The fact that the expression "heteroatom" is widely used and understood by those having ordinary skill in the art is also demonstrated by the fact that 7,289 patents have issued since 1996 using the word "heteroatom." Of these, 2,082 patents use the word "heteroatom" in the claims, thus indicating that the meaning of the word is understood by many examiners, as well as those having ordinary skill in the art. Applicants' use of the word "heteoatoms" in the claims is consistent with its common usage in the literature. In this regard, it should be noted that the specification at page 8, lines 3-17 describes "hetero-atom containing" groups, which may be either acyclic (not cyclic, e.g., linear or branched) or cyclic. Specific examples of heteroacyclic groups include amidino, alkoxy carbonyl, carbamoyl and thiocarbamoyl groups. There is ample evidence in the literature that the expression "heteroatom" is understood to mean an atom other than carbon, most typically nitrogen, sulfur or oxygen, and that the expression "heteroatom-containing

group" clearly refers to an organic moiety containing an atom different from carbon in its main chain or ring.

The Examiner's proposed amendment to the claim is not any more definite than the description for X and Y now in the claims. However, the proposed language would unduly limit the scope of the claims by expressly disclaiming disclosed embodiments, such as compounds wherein X and/or Y are thiocarbamoyl groups. It is requested that the Examiner carefully reconsider the fact that the expression "heteroatom" is commonly used and understood by those having ordinary skill in the art, such that those having ordinary skill in the art would not have any difficulty understanding the meaning of the expression, especially in view of the description and examples set forth beginning at page 7, line 21 and ending at page 9, line 13 of the specification.

The Examiner has stated that the rationale for the dependence of claim 8 on claim 1 is unclear. Applicants disagree. The compound of claim 8 is encompassed by the formula of claim 1 when W is hydrogen, R^c is n-butylene, R^b is n-propylene, R^1, R^2 and R^3 are each hydrogen, n is zero (i.e., Z_n is not present in the compound), R^a is n-propylene, X is hydrogen, and Y is $-C(NH)NH_2$. By making the above-noted substitutions into the formula of claim 1, the formula of claim 8 is directly obtained. Please note that the claims allow W, R^1, R^2, R^3 and X to be hydrogen, R^b and R^c to be n-butylene and n-propylene respectively, and R^a to be n-propylene. Further, claim 1 allows n to be zero, such that Z_n is not present in the compound. Finally, Y may be a hetero-atom-containing group, e.g., a $-C(NH)NH_2$ group. Accordingly, claim 8 is properly dependent from claim 1.

The Examiner has stated that while claim 1 permits "Q" to be a group of the formula XYN-, "there is no indication that either 'X' or 'Y' can be an amidino group." This is not relevant. Those having ordinary skill in the art would understand that compounds in which Q is a guanidino group are encompassed by claim 1. This is all that is required. The patent laws do not require that a generic claim describe all conceivable species.

The Examiner has further stated that "there is not a sufficiently clear 'roadmap' to get from the definition of 'Q' in claim 1, to the guanidino group of claim 8." Those having ordinary skill in the art would understand that the compound set forth in claim 8 is

encompassed by claim 1. The patent laws do not include any requirement that an independent claim provide a "roadmap" to all conceivable species.

Applicants respectfully request that the Examiner carefully consider Applicants' remarks and the claims in view of the relevant patent laws. Upon so doing, it is believed that the Examiner will agree that the definition for X and Y suggested in the Office Action would unjustifiably deprive Applicants of their inventions and allow competitors to copy Applicants' discovery with impunity such as by selecting a compound wherein either X or Y is a thiocarbamoyl group.

In view of the above amendments and remarks, it is respectfully submitted that the claims meet the requirements of 35 U.S.C. §112, second paragraph, such that withdrawal of the rejection is appropriate.

Rejections 35 U.S.C. §102

Claims 1, 2, 5, 6, 8, 19 and 21-23 have been rejected under 35 U.S.C. §102(b) as being anticipated by Cherksey (WO 93/12777). The Examiner has stated that the Cherksey reference teaches (at page 14, lines 16-20) a compound designated "R" which is identical to the compound in claim 8.

Applicants respectfully disagree with this rejection. Although the formula disclosed in the Cherksey '777 reference is identical to the formula in claim 8, the formula disclosed as compound "R" in the Cherksey '777 reference does not constitute a disclosure of a substantially pure compound having the required formula. It is fundamental that to anticipate a claim, the reference must teach every element of the claim. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The Cherksey '777 patent does not teach a substantially pure compound as claimed, either expressly or inherently. Further, the Cherksey '777 patent does not provide an enabling disclosure for preparing a substantially pure compound as claimed. As set forth in Applicants' Declaration Under Rule §1.132, the synthesis "methods described in WO 93/12777 were reproduced exactly in an attempt to synthesize arginine-spermidine and lysine-spermidine, which are analogous to compounds A and B" in WO 93/12777. Mass spectrophotometry analysis showed significant peaks for various starting materials, but did not show any trace of the alleged products, arginine-spermidine or lysine-spermidine. The declarant, Lars E. Sundstrom, stated that it was his opinion that the "results show that arginine-spermidine and lysine-spermidine, if present at all, are present in the final product in an amount less than 1%." Clearly, the results demonstrate that the synthesis methods of Cherksey '777 do not produce the claimed compounds in substantially pure form, and therefore do not meet each and every limitation of the claims. Accordingly, Cherksey '777 does not anticipate the claimed substantially pure compound.

The Examiner has criticized Applicants' evidence that the Cherksey '777 reference does not provide an enabling disclosure for the claimed substantially pure compounds. In particular, the Examiner has stated that "Applicants have not said what their reaction conditions were." This is incorrect. Please note that the Declaration of Lars E. Sundstrom states that the methods described in WO 93/12777 were reproduced exactly. Therefore, contrary to the Examiner's allegation that the declaration is not particularly meaningful, the declaration demonstrates that the methods of WO 93/12777 are not enabling of a substantially pure preparation of the compounds.

The Examiner has also argued that any disclosure of a compound will preempt anyone else from claiming that compound, and "given that the claims are drawn only to compounds and compositions, and to a method of making or using them, the rejection is maintained."

Applicants agree that they cannot claim the compounds disclosed in Cherksey '777. However, the Examiner has mischaracterized the claims by stating that the claims are "drawn only to compounds and compositions, and to a method of making or using them." This underscores the fact that the Examiner has disregarded certain limitations of the claims, namely that the compound must be substantially pure. It is well established that a pure compound

may, under certain conditions, be patentable over the same compound in an impure form. See for example *In re Williams*, 80 USPQ 150 (CCPA 1948). Clearly, the impure compounds of Cherksey '777 do not anticipate the pending claims for substantially pure compounds.

Claims 1, 2, 5, 6, 8, 19 and 21-23 have been rejected under 35 U.S.C. §102(b) as being anticipated by Cherksey (U.S. Patent 5,242,947).

There is not any reason to make a separate rejection under 35 U.S.C. §102(b) for the Cherksey '947 patent. The disclosure in the Cherksey '947 patent and the Cherksey PCT '777 publication are substantially identical. Accordingly, all comments set forth above with respect to WO 93/12777 are applicable with respect to Cherksey '947, and are hereby incorporated. Accordingly, the rejection based on Cherksey '947 should be withdrawn for the reasons set forth above with respect to Cherksey WO 93/12777.

Claims 1, 2, 5, 6, 8, 19 and 21-23 have also been rejected under 35 U.S.C. §102(b) as being anticipated by Cherksey (U.S. Patent No. 5,424,202).

Cherksey '202 is a division of Cherksey '947, and contains an identical disclosure. Accordingly, Cherksey '202 is substantially identical to Cherksey WO 93/12777. Therefore, the remarks set forth above with respect to the Cherksey '777 reference are equally applicable to the Cherksey '202 patent.

It is respectfully submitted that none of the above references anticipate the claimed composition which is substantially pure. Accordingly, withdrawal of these rejections is appropriate.

Rejection Under 35 U.S.C. §103

Claims 1, 2, 5, 6, 8, 19-24 have been rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (WO 93/12777) or Cherksey (U.S. Patent No. 5,242,947) or Cherksey (U.S. Patent No. 5,424,202). The Examiner has admitted that Cherksey failed to optimize reaction conditions and "provides little in the way of discussion of protecting groups." However, the Examiner speculated that an organic chemist of ordinary skill would have recognized that an optimal yield would be obtained if there were just one electrophile and one nucleophile. Thereafter, the Examiner speculated on a synthetic scheme that might

provide high yields of the claimed compounds. Based on this speculation alone, the Examiner concluded that "the claims are rendered obvious."

The Examiner's proposed synthesis scheme does not suggest appropriate solvents, reaction conditions, etc., and therefore lacks sufficient detail to enable preparation of the claimed substantially pure compounds without undue experimentation. Accordingly, the rejection relies on non-enabled speculation, rather than on prior art and legitimate motivation for modifying the teachings of Cherksey. An obviousness rejection may not rely on speculation as to what those having ordinary skill in the art might know as a substitute for prior art (*In re Lee*, Fed. Cir. No. 00-1158, 1/18/02).

The Examiner has stated that "once presented with the structure of the target compound, the organic chemist of ordinary skill could obtain the compound within the bounds of routine experimentation. While this is true in some cases, it is not necessarily the case that those having ordinary skill in the art would be motivated or capable of producing the target compound in substantially pure form. A person of ordinary skill in the art attempting to prepare the compounds of the Cherksey references would naturally follow the preparation methods disclosed in those references, and thus would obtain impure compounds. Without incentive to produce pure compounds, it would not be obvious to modify the disclosed preparation conditions or to introduce purification methods so as to produce pure compounds.

In view of the above remarks, it is respectfully submitted that the claimed substantially pure compounds would not have been obvious based on the teachings of the Cherksey references. Accordingly, withdrawal of the rejection is appropriate.

Claims 1-24 have been rejected under 35 U.S.C. §103 as being unpatentable over Cherksey (WO 93/12777) or Cherksey (U.S. Patent No. 5,242,947) or Cherksey (U.S. Patent No. 5,424,202). This rejection is inappropriate. First, the rejection is directed to claims which are not currently under consideration. Second, with respect to the claims under consideration, this rejection is a repeat of the previous rejection with additional comments relating to purification by chromatographic methods. In this regard, the Examiner has stated that HPLC may be effective at separating two or more compounds which have nearly the same polarity. While HPLC may be a powerful tool for separating components having very similar physical and chemical properties, this does not provide a teaching, suggestion or motivation

for preparing the substantially pure compounds as claimed. In other words, the alleged utility of HPLC taken together with the teachings of the Cherksey references would not provide proper motivation for modifying the methods of Cherksey to achieve the substantially pure compounds as claimed. Accordingly, withdrawal of the rejection is appropriate.

CONCLUSION

In view of the above amendments and remarks, it is respectfully submitted that the application is in condition for allowance and notice of the same is earnestly solicited.

Respectfully submitted,

LARS E. SUNDSTROM ET AL.

By: Price, Heneveld, Cooper, DeWitt & Litton

July 24, 2002
Date

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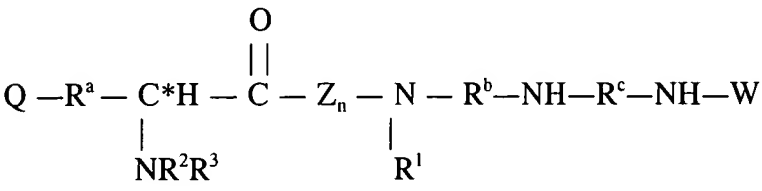
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 19 and 23 have been amended as follows:

1. (Twice Amended) A substantially pure compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group[s], or [simple] hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents [a] α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

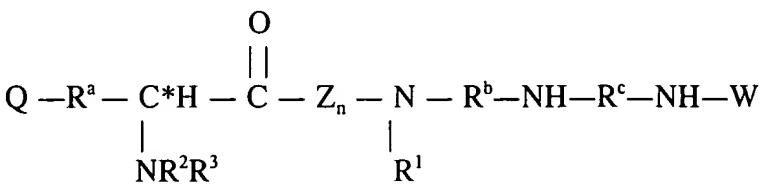
R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents [a] α, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents [a] α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof.

19. (Amended) A composition consisting essentially of a compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group[s], or [simple] hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents [a] $\underline{\alpha}$, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

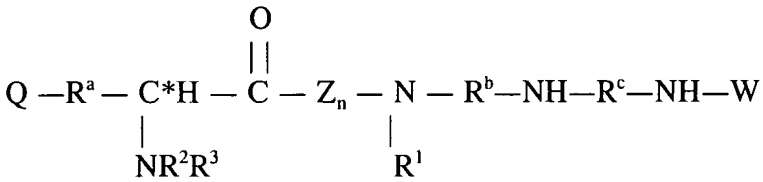
R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents [a] $\underline{\alpha}$, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents [a] $\underline{\alpha}$ are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof.

23. (Amended) A non-toxic composition consisting essentially of a compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group[s], or [simple] hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents [a] $\underline{\alpha}$, defined below;

the chiral carbon atom indicated by the asterisk is in the $\underline{L}$ configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents [a] $\underline{\alpha}$, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents [a] α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof.